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# Gender difference in pain presentation among patients with acute coronary syndrome: A systematic review and meta-analysis

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## ABSTRACT

**Background:** Acute coronary syndrome is the leading cause of death worldwide. Chest pain is vital for immediate diagnosis and intervention. Few studies evaluated the effect of gender on chest pain in the setting of acute coronary syndrome. This meta-analysis assessed gender differences among patients with acute coronary syndrome. **Methods:** We searched three databases for relevant articles. The searching engine was limited to the period from January 2013 up to January 2023. The keywords acute coronary syndrome, typical chest pain, atypical chest pain, clinical characteristics, gender differences and sex differences were used. **Results:** Out of the 933 studies, 811 were eligible after the removal of duplication, of them, 64 full texts were screened and only seven studies were included in the final analysis (27886 patients (20301 males and 7585 males)). No difference was evident between women and men regarding chest pain as a symptom of the acute coronary syndrome (odd ratio, 1.24, 95 CI, 0.91-1.70, P-value for overall effect, 0.18). Substantial heterogeneity was found I<sup>2</sup> for heterogeneity, 91%, the Chi-square, 64.76, the mean difference=6. In addition, atypical chest pain was not different between males and females (odd ratio, 0.72, 95 CI, 0.48-1.08, P-value for overall effect, 0.11). Substantial heterogeneity was found I<sup>2</sup> for heterogeneity, 92%, the Chi-square, 39.48, the mean difference=3. **Conclusion:** No significant difference was evident across gender regarding chest pain (typical or atypical) among patients with acute coronary syndrome. Future research on diagnostic tools for acute coronary syndrome and focusing on sex differences in chest pain presentation are needed.

**Keywords:** Acute coronary syndrome, chest pain, gender differences.

## 1. INTRODUCTION

Despite the substantial improvement in the diagnosis, cardiovascular disease remained the leading cause of mortality over the globe, with one in two due to ischemic heart disease (Bergmark et al., 2022). Acute coronary syndrome

accounts for 7 million annual death and 129 million disability adjusted life years and a substantial economic burden (Thygesen et al., 2018). Acute coronary syndrome is classified as unstable angina (symptoms of acute coronary syndrome present without biochemical evidence) or types 1 myocardial infarction (ST-segment elevation of non-ST-segment elevation) with biochemical evidence by troponin or other cardiac biomarkers, in addition to other evidence including symptoms, supporting ECG or evidence of a coronary thrombus (White et al., 2019). Type 2 myocardial infarction results from demand and supply mismatch and is associated with a higher mortality rate (Killip and Kimball, 1967).

Pain is an essential pointer to a possible diagnosis of the acute coronary syndrome, which needs confirmation by cardiac biomarkers and ECG findings and physical examination are usually non-specific. However, it is important for risk stratification (Ralapanawa and Sivakanesan, 2021). Chest pain accounts for 5% of emergency visits (various causes from cardiopulmonary or referred pain), of which only five percent are due to serious life-threatening diseases including acute coronary syndrome (NCHS, 2017; Hsia et al., 2016; Stepinska et al., 2020; Musey et al., 2021; Umalkar et al., 2022).

Previous studies reported a sex disparity and increased mortality among women with acute coronary syndrome, the difference in clinical presentation and delayed access to reperfusion facilities are to blame (Graham et al., 2017; Conradie et al., 2022). Women are more likely to have normal coronary arteries and a higher probability of non-obstructive coronary artery syndrome, coronary artery spasms and Takotsubo syndrome (Humphries et al., 2017; Canto et al., 2012). The clinical presentation of acute coronary syndrome between genders was discussed controversially. Therefore, we went ahead to compare gender differences in pain among patients with the acute coronary syndrome.

## 2. METHODOLOGY

### Study design

This study is a systematic review and meta-analysis that was adherent to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015).

### Eligibility Criteria according to PICOS

#### *Inclusion criteria*

We included if they were cross-sectional, case-control, retrospective and prospective cohorts. The studies were eligible if they were published in the English language during the period from January 2013 up to January 2023. The studies were included if they reported chest pain (typical or atypical) among women and men with the acute coronary syndrome.

#### *Exclusion criteria*

Case reports and case series were not included.

### Outcome measures

Chest pain (typical or atypical) among women and men with the acute coronary syndrome. Studies on the acute coronary syndrome in the young age, elderly, partial bundle branch block or only ST-Segment elevation myocardial infarction were not included because they are not reflecting the real-world clinical setting.

### Information sources and search

Two authors independently searched the Cochrane Library, PubMed, Medline and the first hundred articles in Google Scholar. The search was conducted during January 2023 and was limited to the period from January 2013 up to January 2023. The keywords acute coronary syndrome, typical chest pain, atypical chest pain, clinical characteristics, gender differences and sex differences, males, females, women, men were used with protean "AND" or "OR". Any discrepancy between the two authors was solved by agreement. Chest pain character among women and the author's name, number of patients and events were collected and entered in an excel sheet. A modified Newcastle Ottawa Scale assessed the quality of the included study (Norris et al., 2021) (Figure 1) (Tables 1, 2, 3).

### Ethical considerations

An ethical approval for conducting the study was obtained from the Najran University Faculty of Medicine Committee of Scientific Research and Conferences, No.:444-42-41290-DS.

Data analysis

The RevMan system for meta-analysis (version. 5.4) was used and the data were all dichotomous and entered manually. The random effect was used because of the significant heterogeneity. Funnel plots were used to assess lateralization. A P-value of <0.05 was considered significant for the overall effect and the Chi-square test.

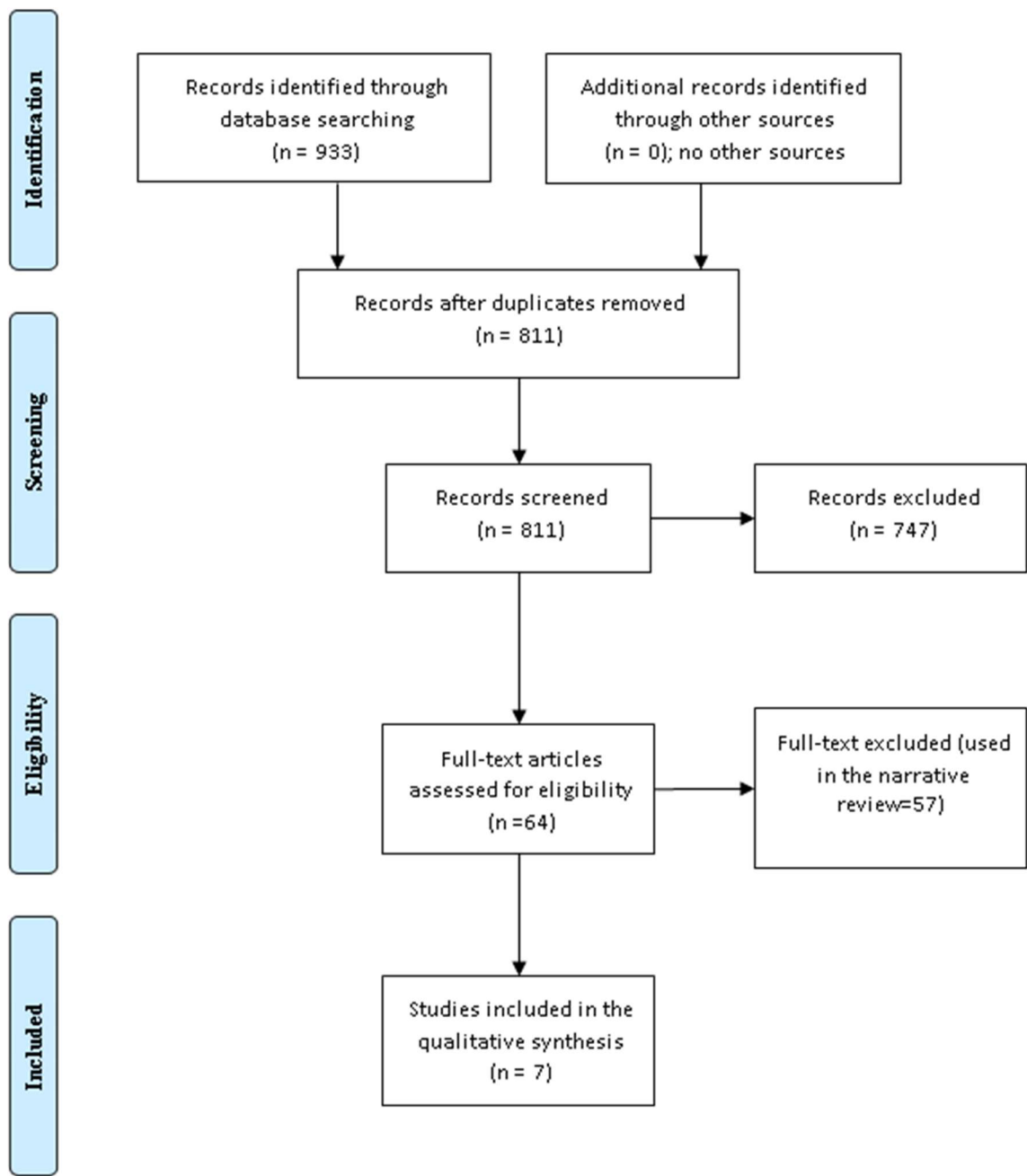


Figure 1 Chest pain among males and females with acute coronary disease (The PRISMA Chart)

Table 1 Quality assessment of the included studies

Reference	Selection	Compatibility	Outcome	Overall
Ferry et al., (2019)	3	2	3	8
Guo et al., (2022)	3	2	2	7
Khan et al., (2010)	3	2	3	8
Lichtman et al., (2018)	4	2	2	9
Rubini-Gimenez et al., (2014)	3	2	2	7
Shehab et al., (2020)	3	1	3	7

Wouters et al., (2021)	3	2	2	7
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**Table 2** Gender differences in presentation with typical chest pain

Author	Country	Type of study	Number	Females	Significance
Ferry et al., (2019)	UK	Prospective	1081/1185	698/756	Not significant
Guo et al., (2022)	Brazil	Retrospective	2432/2778	1553/1833	Higher among males
Khan et al., (2010)	Nigeria	Prospective	54/64	43/64	Higher among males
Lichtman et al., (2018)	USA	Prospective	874/976	1748/2009	Not significant
Rubini-Gimenez et al., (2014)	Multi-nations	Prospective	1147/1679	575/796	Not significant
Shehab et al., (2020)	Gulf countries	Retrospective	12174/13 499	1681/2033	Lower among females
Wouters et al., (2021)	Netherlands'	Cross-sectional	110/120	81/85	Higher among females

**Table 3** Gender differences in presentation with atypical chest pain

Author	Country	Type of study	Males	Females	Significance
Ferry et al., (2019)	UK	Prospective	413/1185	224/765	Not significant
Khan et al., (2010)	Nigeria	Prospective	10/64	21/64	Higher among females
Lichtman et al., (2018)	USA	Prospective	490/976	1236/2009	Not significant
Rubini-Gimenez et al., (2014)	Multi-nations	Prospective	741/1679	308/796	Not significant

### 3. RESULTS

#### Characteristics of the included studies

Out of the 933 studies, 811 were eligible after the removal of duplication, of them, 64 full texts were screened and only eleven cohorts from seven studies were included in the final analysis (Table 1). In this meta-analysis, seven studies (Ferry et al., 2019; Khan et al., 2010; Guo et al., 2022; Lichtman et al., 2018; Rubini-Gimenez et al., 2014; Shehab et al., 2020; Wouters et al., 2021) (included 27886 patients (20301 males and 7585 males)). The total events were 3173. The studies were five prospective, one cross-sectional and one retrospective, they were from Europe (three), the USA, Africa, Asia and South America (one each).

#### Chest pain (typical and atypical) among females and males with acute coronary syndrome

Seven cohorts (Table 1, 2) addressed the prevalence of chest pain among men and women with acute coronary syndrome (Ferry et al., 2019; Guo et al., 2022; Khan et al., 2010; Lichtman et al., 2018; Rubini-Gimenez et al., 2014; Shehab et al., 2020; Wouters et al., 2021). No difference was evident between women and men regarding chest pain as a symptom of the acute coronary syndrome (odd ratio, 1.24, 95 CI, 0.91-1.70, P-value for overall effect, 0.18). Substantial heterogeneity was found I<sup>2</sup> for heterogeneity, 91%, the Chi-square, 64.76, the mean difference=6 (Figure 2). While four cohorts investigated atypical chest pain (Ferry et al., 2019; Khan et al., 2010; Lichtman et al., 2018; Rubini-Gimenez et al., 2014). Similarly, males and females equally presented with atypical chest pain (odd ratio, 0.72, 95 CI, 0.48-1.08, P-value for overall effect, 0.11). Substantial heterogeneity was found I<sup>2</sup> for heterogeneity, 92%, the Chi-square, 39.48, the mean difference=3 (Figure 3).

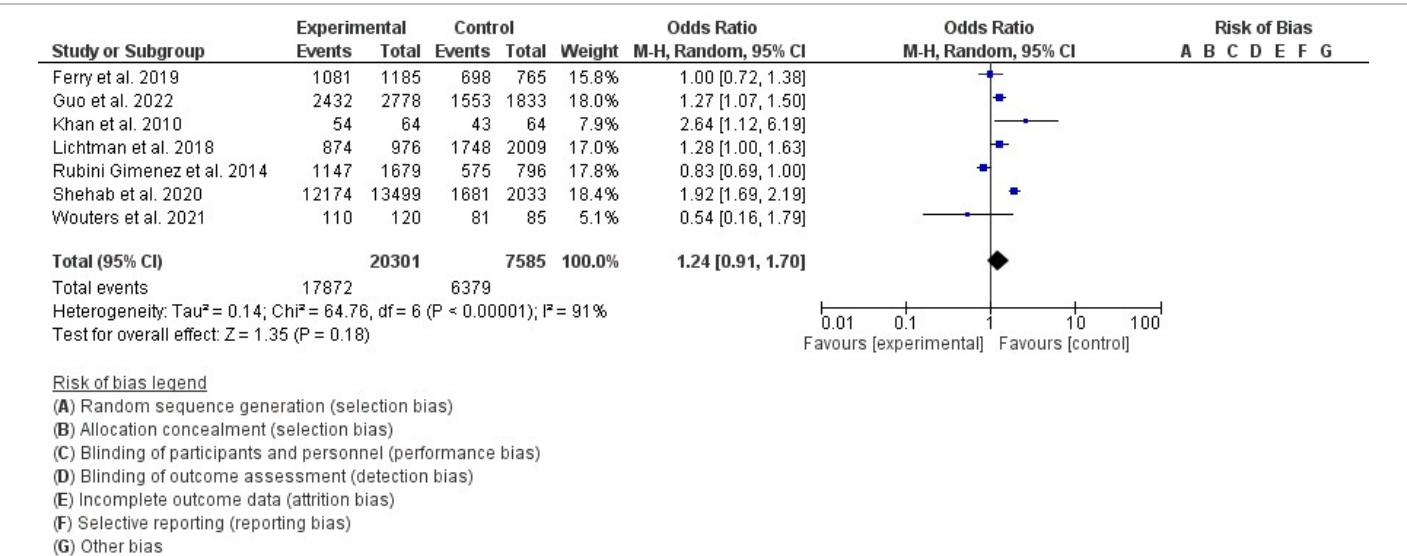


Figure 2 (A) Gender differences in presentation with typical chest pain (forest plot)

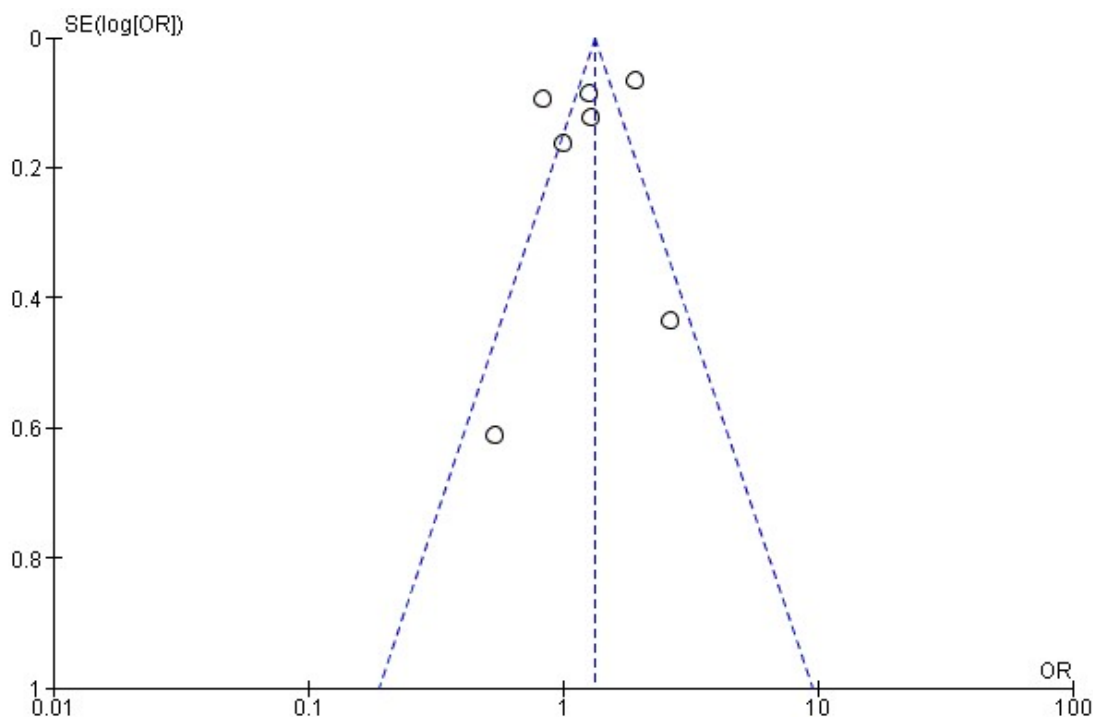


Figure 2 (B) Gender differences in presentation with typical chest pain (funnel plot)

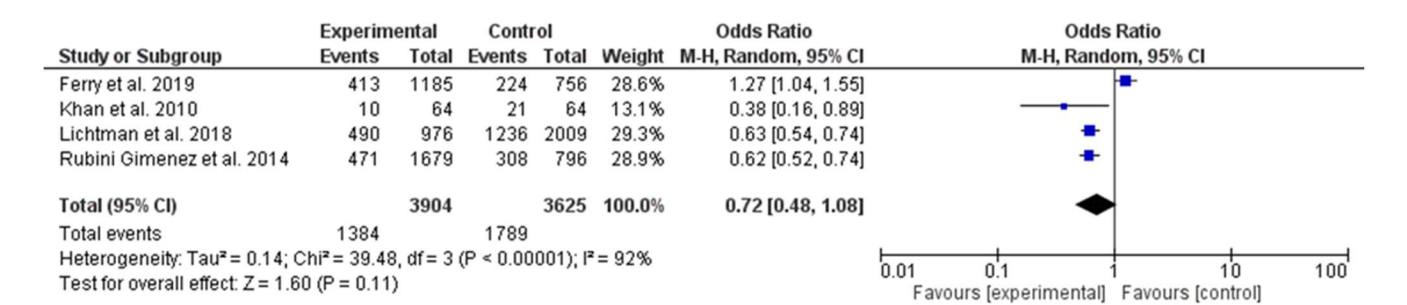


Figure 3 Gender differences in presentation with atypical chest pain

## 4. DISCUSSION

Women lag by twenty years behind males regarding acute coronary syndrome. However, they had a higher rate of mortality (Arora and Bittner, 2015). Chest pain is vital for the diagnosis of acute myocardial infarction and is linked to outcomes; in addition, chest pain substantially influenced the time from onset to the presentation to the emergency department (Canto et al., 2012). A patient who presented without chest pain is more prone to hospital mortality (Gupta et al., 2015). In this meta-analysis, no significant difference was evident in chest pain presentation among males and females with acute coronary syndrome. Similarly, women were less likely to present with atypical chest pain (odd ratio, 1.24, 95 CI, 0.91-1.70 and 0.72, 95 CI, 0.48-1.08 respectively). The current findings contradict Shin et al., (2010) who reported that women were more probably to present with back pain, nausea and vomiting. Another meta-analysis Gillis et al., (2014) showed that men were more probably to present with chest pain in line with the present findings in which no differences were evident in chest pain presentation. The authors reported a higher prevalence of atypical symptoms among women in contradiction to the present results. Importantly, Gillis et al., (2014) assessed only acute coronary syndrome among the elderly population. Chest pain characterization is a simple, readily available symptom and constituted a major cornerstone in the diagnosis of acute myocardial infarction. In addition, chest pain is vital for subsequent diagnosis and management (Lichtman et al., 2018). The different presentation of chest pain among women might lead to misdiagnosis, delayed diagnosis, a lower benefit from revascularization if needed and high mortality (Lawesson et al., 2013). The current findings are contradicting a previous meta-analysis that showed less chest pain among women (Coventry et al., 2011). However, the authors reported that women were more probably to present with neck and right arm pains similar to the current findings. The difference in pain character across gender might be explained by hypercoagulability and estrogen influence (Chaudhary et al., 2022). The current review updates the few previous meta-analyses and included recent studies (Coventry et al., 2011; Canto et al., 2007; Oosterhout et al., 2020). In addition, the findings were more specific by restricting the analysis to chest pain and excluding studies on particular types of acute coronary syndrome and avoiding the limitation to a specific age group. Our finding avoided including the young due to the difference in pathophysiology: Women are more likely to present with type 2 acute coronary syndrome than men are; furthermore, plaque erosion is commoner among women in contrast to plaque rupture (McSweeney et al., 2016; Yahagi et al., 2015; Chandrasekhar and Mehran, 2016; Burke et al., 1998). The strength of the current meta-analysis is the inclusion of all age groups and all types of the acute coronary syndrome (reflecting the real clinical presentation). However, the study was limited by the few studies included and the significant heterogeneity observed.

## 5. CONCLUSION

Presentation with chest pain (atypical or typical) was equal among males and females with acute coronary syndrome. Future research on diagnostic tools for acute coronary syndrome and focusing on sex differences in chest pain presentation are highly needed.

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**Author contributions:** All the authors contributed equally in this meta-analysis.

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This study has not received any external funding.

### Conflict of interest

The authors declare that there is no conflict of interests.

### Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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